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Modeling the progression of Parkinson's Disease: comparison of subjects with and without Sleep Disorders

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Estimating a model of disease progression at the very early stage of PD is a major challenge to track disease progression and measure the outcome of therapeutic interventions. Using an advanced statistical learning approach, we aim to estimate temporal dynamics of occurrence of motor signs in idiopathic REM Sleep Behavior Disorder. The data come from repeated observations in time of sub-scores of the MDS-UPDRS scale. Subjects are extracted from PPMI prodromal cohort, which

focused on patients with Sleep Behavior Disorders (RBD). PPMI Control cohort is also used to extract cutoffs values of abnormalities for the motor subscores. The model learns a typical group-average trajectory characterizing the progression of clinical scores. We focus on the estimated group-average trajectory that models the joint progression of motor sub-scores, and extract times of intersections with sub-scores abnormal values. We bootstrap the process and

compute bootstrap densities of abnormality's occurrence timings. Finally we show the distribution of their occurrence time before conversion to Parkinson's Disease.

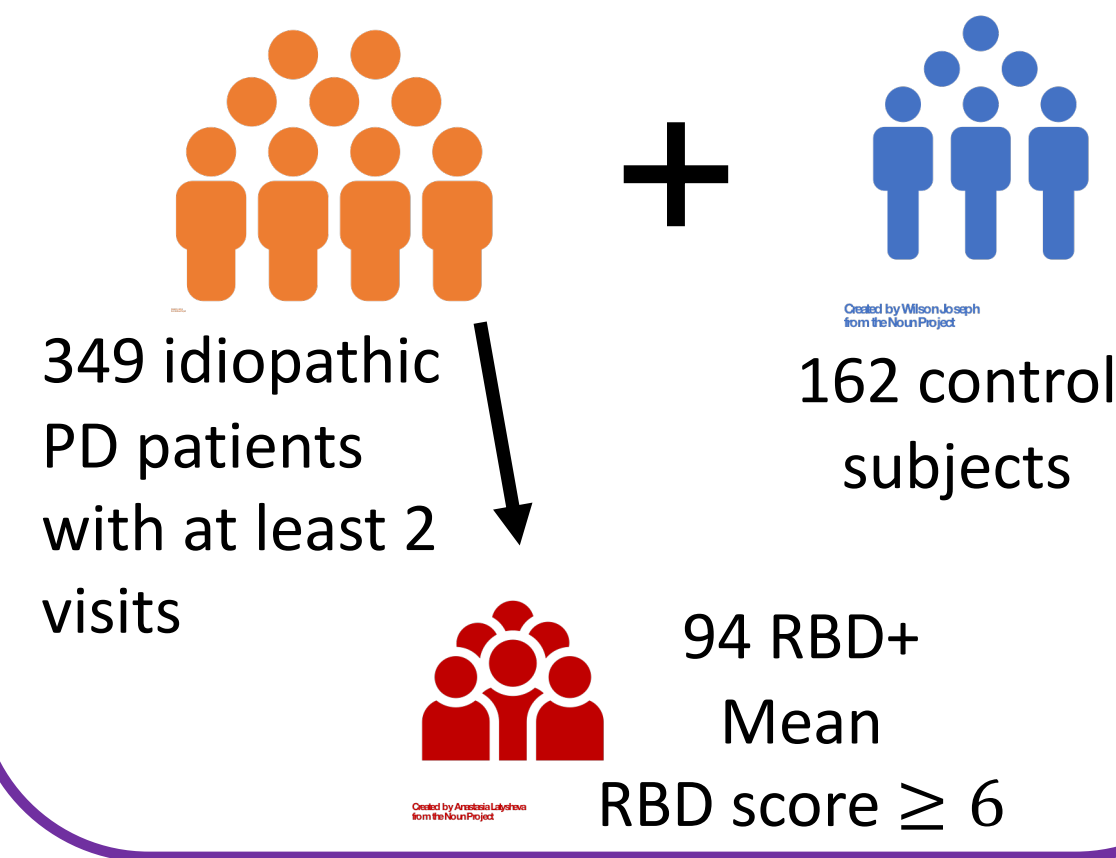
Data

PPMI PD Dataset – longitudinal observational cohort

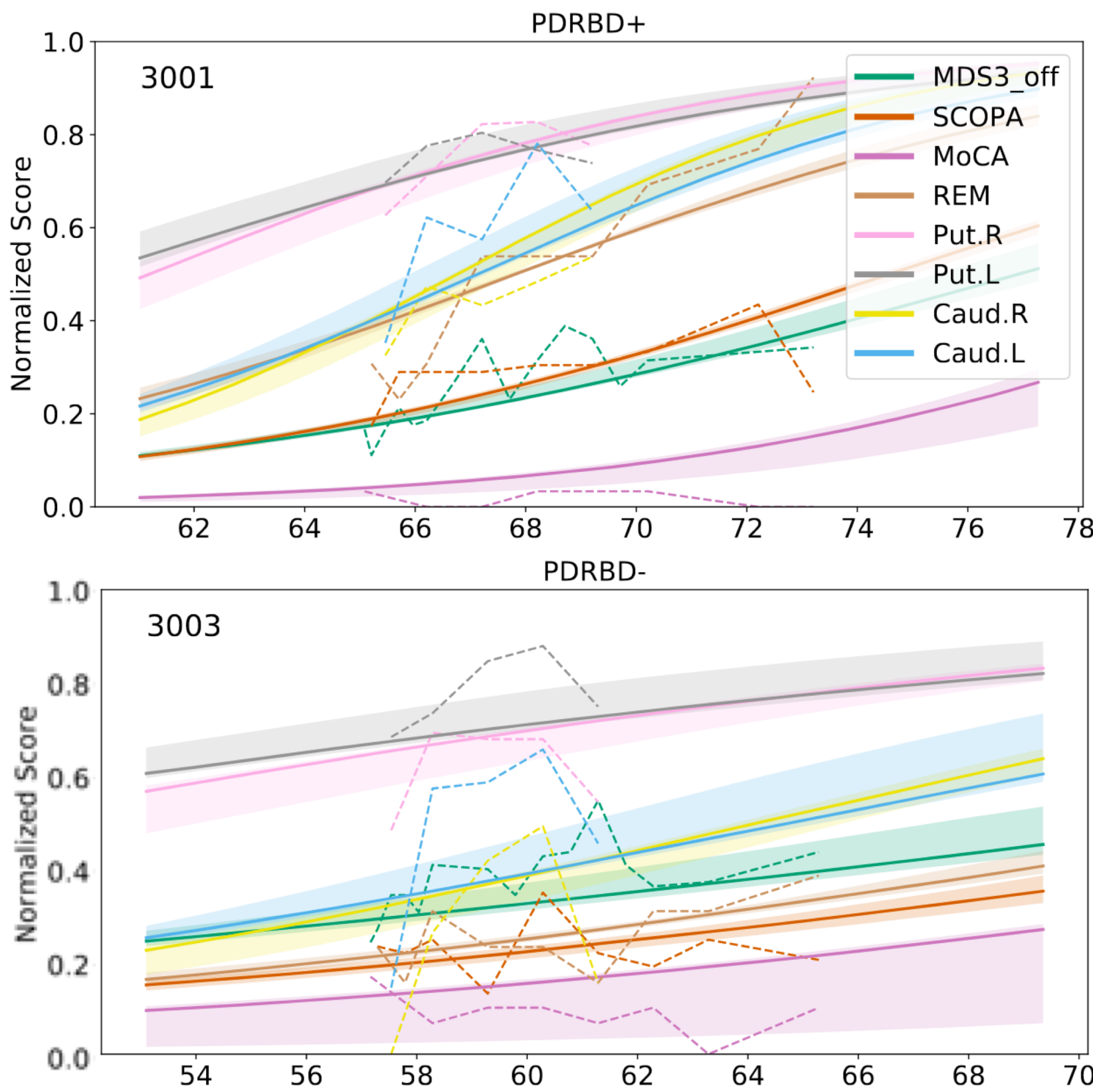
8 Features

- MDS-UPDRS part III - motor examination
- MoCA - cognitive examination
- SCOPA-AUT - dysautonomia questionnaire
- REM - RBD questionnaire
- 4 dopamine measurements - DatScan
 - Putamen Right
 - Putamen Left
 - Caudate Right
 - Caudate Left

Patient Selection



Example of two subjects



Data normalisation between 0 and 1

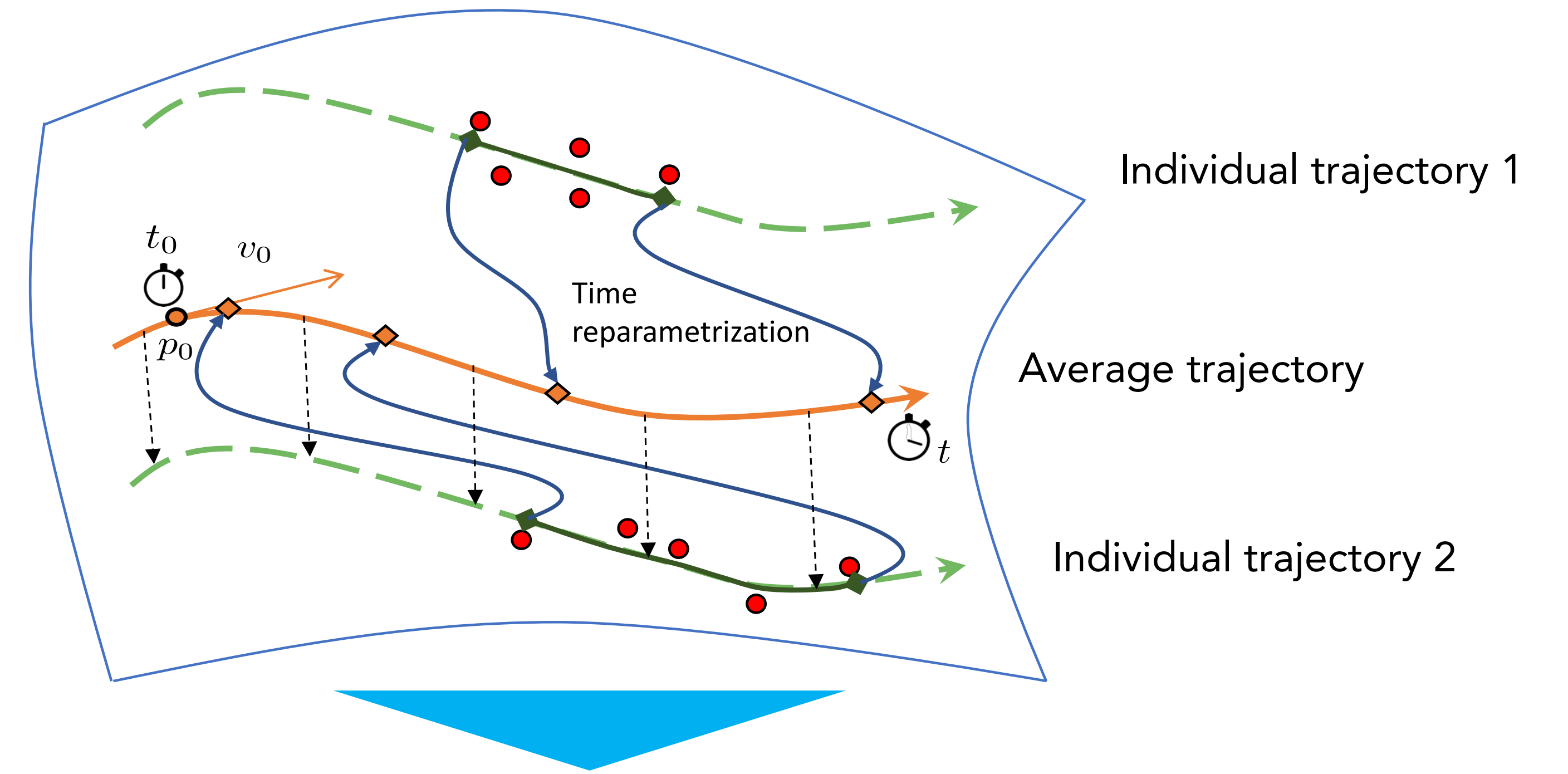
- 0 = best possible value
- 1 = worst possible value

A PD patient will slowly evolve over time from values near 0 to values near 1.

Methods

Generic spatio-temporal model for longitudinal data

We use a generic mixed-effects model for longitudinal manifold-valued data [Schiratti et al, 2015]. The model allows to estimate an *average trajectory* as well as *individual trajectories*. Individual trajectories are modeled as parallel variations of the average trajectory in the manifold. Random effects characterize *spatial variation* (which parallel curve is followed, in green), as well as *temporal variations* (blue arrows). Each individual trajectory is reparameterized in time with an affine transformation, estimating from the data an onset and a speed of progression.



Multivariate logistic model

$$y_{i,j,k} = \left(1 + \left(\frac{1}{p_k} - 1 \right) \exp \left(- \frac{\alpha_i v_k (t_{i,j} - t_\theta - \tau_i) + (w_i)_k}{p_k (1 - p_k)} \right) \right)^{-1} + \epsilon_{i,j,k}$$

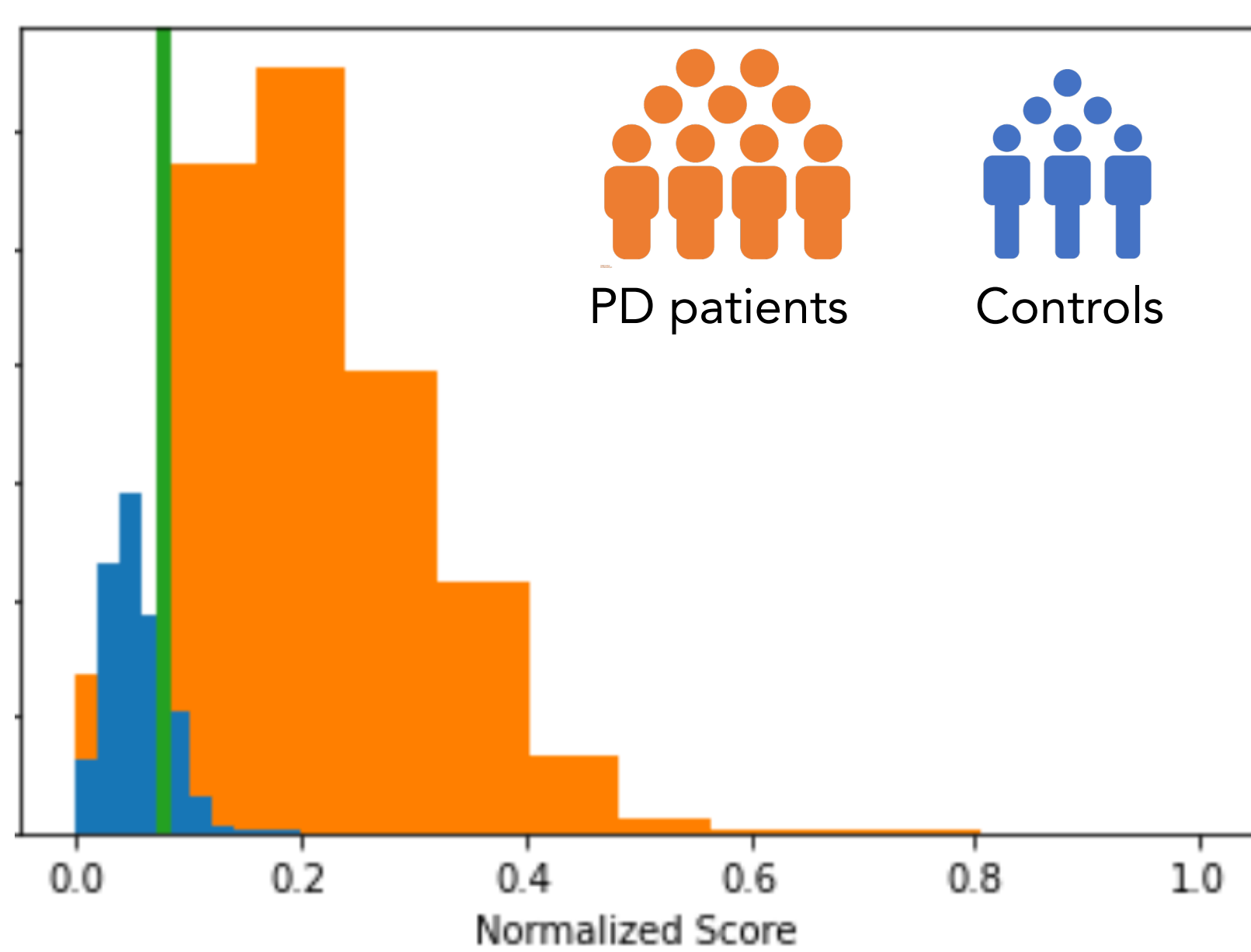
- Non linear mixed-effect model
- Defined for $t_{i,j}$, but also any t
- Generative mixed-effects model
- Handle missing values

Parameters estimation : MCMC-SAEM algorithm

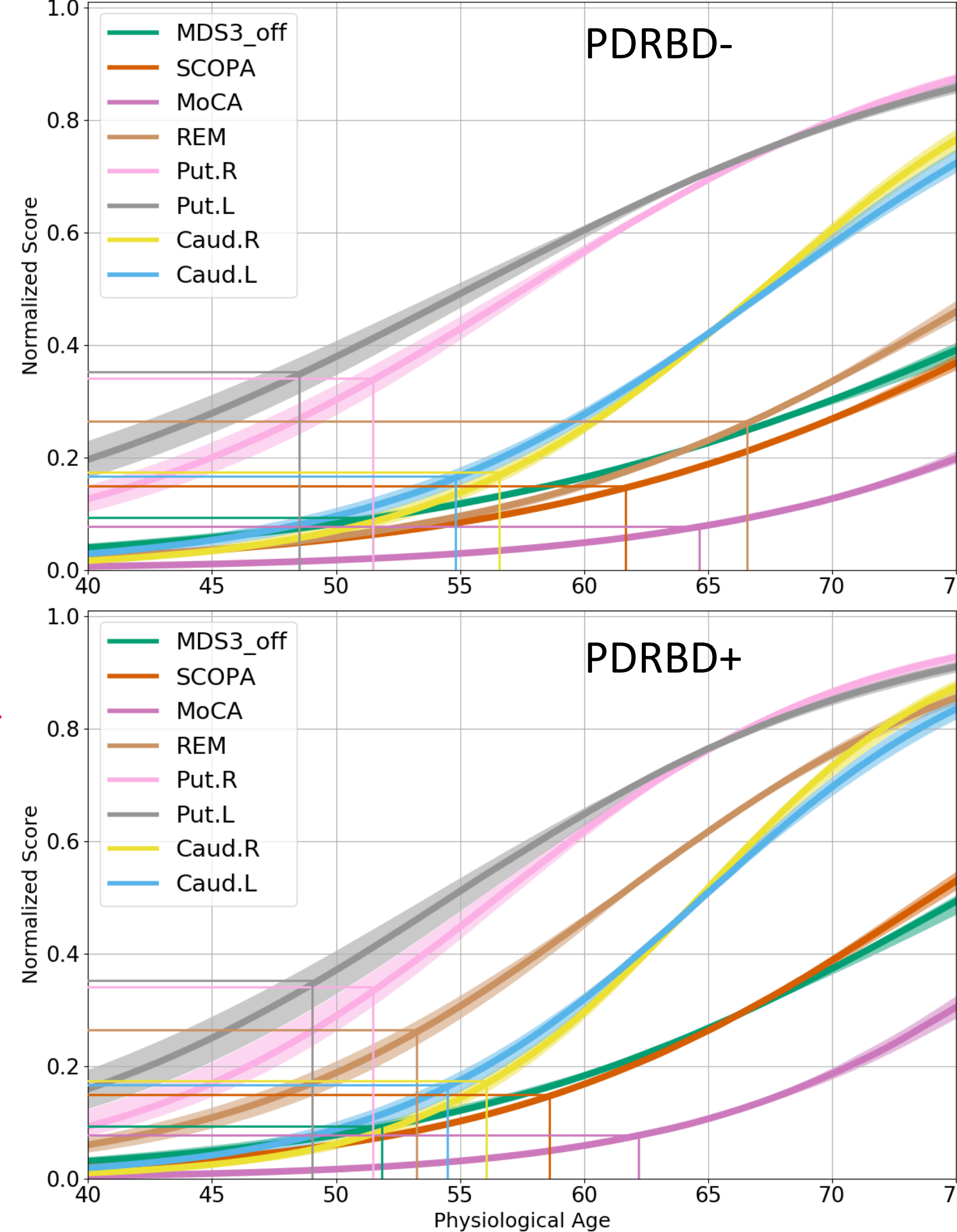
Results

- Abnormality thresholds computation for each biomarker using balanced logistic regression between PD and control subjects at baseline.
- From a set of patients, we can estimate an average trajectory of biomarker progression according to time. To get abnormalities onset ages, we look at the times where each cutoff is reached.
- The two group are then compared based on their respective abnormalities onset ages. The process is cross-validated (10 x 5-fold CV) across patients to obtain bootstrap estimations.

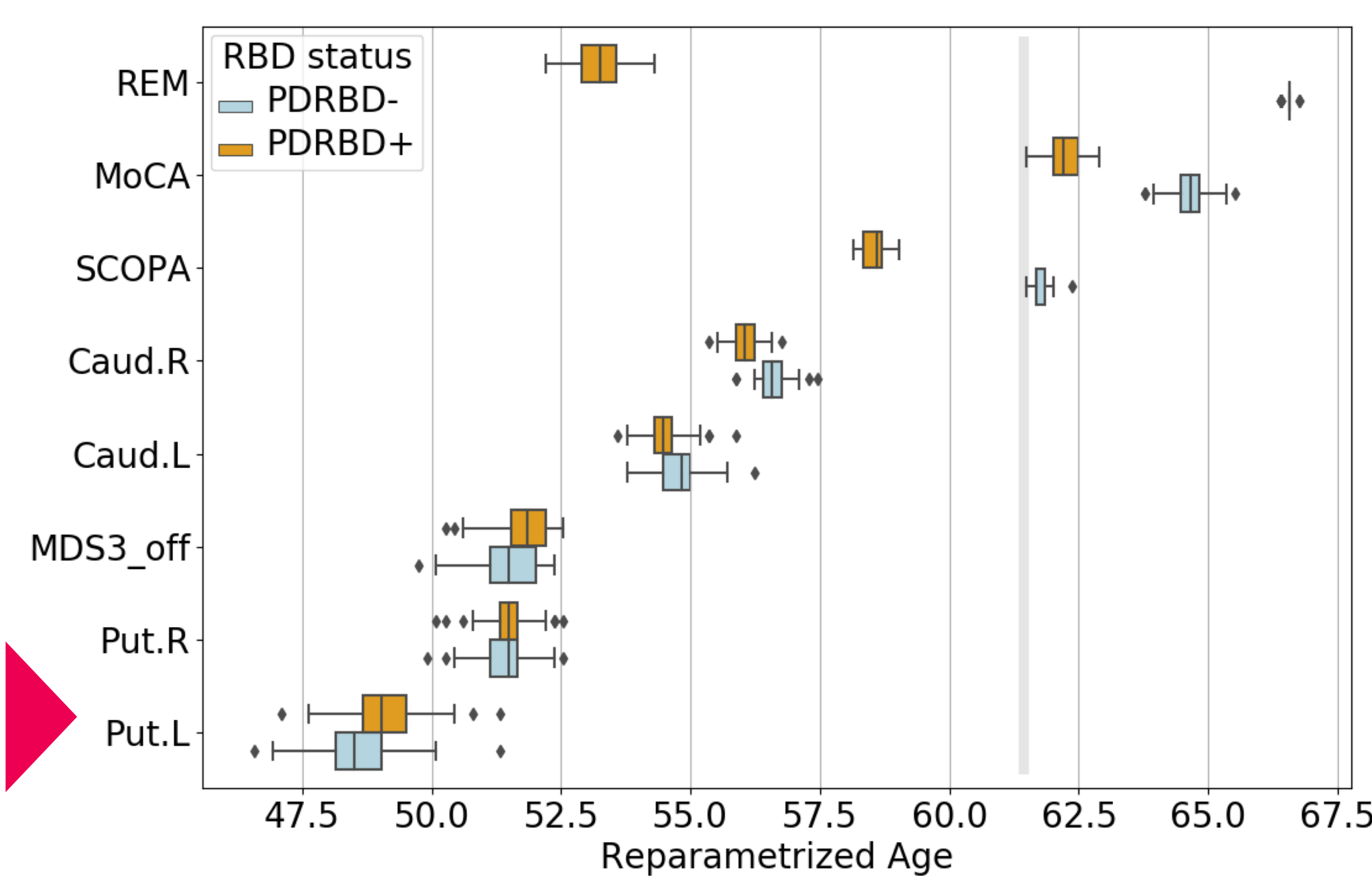
1. Abnormality threshold computation



2. Average trajectory per group & abnormality onset



3. Group comparison



10 x 5-fold CV => « Bootstrap estimation » of average age of abnormality onset.

Significant differences in dysautonomia (SCOPA-AUT) and cognitive impairments (MoCA).

- Dysautonomia:** PDRBD- patients become abnormal in average near the diagnosis while PDRBD+ patients become so 3 years before diagnosis.
- Cognitive impairments:** PDRBD- patients become abnormal 3.2 years after the diagnosis while PDRBD+ patients become so 0.8 years after the diagnosis.

Conclusion

We were able to assess the progression of biomarkers on the PPMI PD cohort using a longitudinal model with patient's specific reparametrizations in time. As the highest variance of space-shift w_i is found in sleep, we study differences between PDRBD+ patients and PDRBD-. PDRBD+ show **evidence of dysautonomia in average 3 years before diagnosis**, whereas PDRBD+ patients become abnormal shortly after. To a lesser extent, MoCA also becomes abnormal earlier in PDRBD+. In comparison, imaging biomarker and MDS-UPDRS part III show no differences between PDRBD+ patients and PDRBD- patients.

References

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